DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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SEP 23 2002

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
And by Facsimile Transmission

CBER – 02– [redacted]

Warning Letter

Ronald G. Crystal, M.D.
515 East 71st Street
New York City, New York 10021

Dear Dr. Crystal:

During the period from April 17 though April 24, 2002, Mr. Thomas P. Hansen, an investigator with the Food and Drug Administration (FDA), reviewed your conduct of a clinical study entitled [redacted] The inspection was conducted under the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs. A Form FDA 483, List of Inspectional Observations, was issued to you and discussed with you at the conclusion of the inspection.

We have reviewed your written response dated May 2, 2002, addressed to the FDA New York District Office, to the Form FDA 483, and have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR) Parts 50 and 312 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation.

1. **You failed to ensure that the investigation was conducted according to the investigational plan (protocol). [21 CFR § 312.60].**

   A. You failed to follow the protocol by enrolling subjects who did not satisfy the eligibility criteria. You enrolled a total of — subjects in the study. None of the — subjects met the criteria for inclusion. You administered the investigational product to subjects who should have been excluded, as described below.

i. None of the [redacted] subjects enrolled in the study have documentation of [redacted] infection status, [redacted] of the [redacted] subjects have no documentation of [redacted] infection status, [redacted] subjects have no documentation of [redacted] status, and [redacted] subjects have elevated Erythrocyte Sedimentation Rates. Section 3.2 of the protocol requires "no evidence of active infection of any type" for a person to be included in the study.

ii. Subject [redacted] was enrolled in the study without Computerized Tomography (CT) documentation of the number of [redacted] present at the time of enrollment. Section 3.2 of the protocol requires that the subject have two or more [redacted] detected by CT scan.

iii. Subject [redacted] had an elevated cholesterol value of 273 mg/dl. Section 3.2 of the protocol requires normal hepatic synthetic function, including cholesterol.

iv. Subject [redacted] was enrolled in the study with a solitary [redacted] lesion and an elevated serum albumin of 5.4 g/dl. Section 3.2 of the protocol requires a subject to have two or more [redacted] detected by CT scan and normal hepatic synthetic function, including serum albumin.

v. Subjects [redacted] and [redacted] were [redacted] years old when enrolled in the study. Section 3.2 of the protocol in effect at the time of their enrollment requires a subject to be between 18 and 70 years old.

Your response acknowledges these violations. Although your response claims that you amended the protocol on July 2, 1996, to remove an upper age limitation, the IRB did not approve this protocol amendment until October 22, 1996, after these subjects were administered the investigational drugs.

vi. Subject [redacted] did not have a confirmatory report of [redacted] carcinoma by histologic diagnosis, which is required by Section 3.2 of the protocol.

vii. Subject [redacted] received Mitomycin-C less than 4 weeks prior to vector administration. Section 3.2 of the protocol requires that subjects not receive chemotherapy at least 4 weeks prior to study entry.

We note that you authored and signed a separate Memorandum to the File dated March 15, 2002 for each of the — enrolled subjects. In each Memorandum, you acknowledge the above issues relating to eligibility criteria for each subject. While we recognize that you documented these deficiencies, we note that these memoranda were not written until March 15, 2002, after you were contacted by the FDA in February 2002 to schedule this inspection.

B. You failed to follow the time intervals for treatments specified in the protocol. Section 3.1 of the protocol and the table entitled — required that — be administered daily from Day 2 until laparotomy, and that laparotomy be scheduled between Days 12 and 15.

i. Subject — had surgery performed on day 9 of the study after receiving 8 days of — therapy.

ii. Subject — had surgery performed on day 8 of the study after receiving 7 days of — therapy.

In your response letter you state, "It should be noted that the trial was designed to be superimposed on the patients' routine medical care. As such, if the clinicians caring for the patients deemed it necessary to move up the surgery, this was done." The subjects' records do not document the need for surgery to be scheduled earlier than the time period required by the protocol.

C. Subject — signed an informed consent form for Part B of the study. The subject was enrolled in Part A which requires surgery, while Part B does not. Subject — had surgery on —

Your response letter acknowledges that subject — signed the incorrect consent form.

2. **You failed to maintain adequate records of the disposition of the drug. [21 CFR § 312.62(a)].**

You failed to maintain adequate records of the disposition of the test article — including quantity received, quantity used, lot number, administration to subjects, and the amount of stock remaining.

In your response letter, you acknowledge the lack of drug accountability records retained during the course of this study, and state your commitment to maintaining these records in the future.

3. **You failed to prepare and maintain adequate and accurate case histories. [21 CFR § 312.62(b)].**

   A signed informed consent form could not be located for Subject —.

   Your response letter acknowledges this violation.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study. It is your responsibility as the clinical investigator to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

Your response letter describes several corrective actions you have implemented to correct these violations and to ensure that all applicable regulations and guidelines are followed for future studies. In addition, your response letter describes changes at the Institute of Genetic Medicine (IGM). The IGM has instituted new Standard Operating Procedures (SOP's) for clinical trials and hired additional personnel.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, and/or the commission of other violations, may warrant the initiation of enforcement actions without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

In light of the corrective actions that you described in your response letter, no response to this letter is required. However, if you do choose to respond to this letter, please send your written response to:

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Telephone: (301) 827-6221

We also request that you send a copy of any response to the FDA District Office listed below.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and
Research

cc: Jerome G. Woyshner, Director
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

David A. Behrman, DMD, Chair
Institutional Review Board
New York Hospital-Cornell Medical Center
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